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**ΘΕΜΑ:**

# Εξάρτηση από την νικοτίνη και απώλεια αυτονομίας μεταξύ Ελλήνων εφήβων καπνιστών: συγχρονική μελέτη σε όλη την επικράτεια

# Nicotine dependence and loss of autonomy among Greek adolescent smokers: a countrywide cross-sectional study

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## ΠΕΡΙΛΗΨΗ

**Εισαγωγή:** Η εξάρτηση από την νικοτίνη αποτελεί την κύρια αιτία του καπνίσματος μεταξύ εφήβων. Η απώλεια αυτονομίας (ΑΑ) θεωρείται η επιτομή της εξάρτησης. Ελάχιστα γνωρίζουμε για την ΑΑ των Ελλήνων εφήβων.

**Στόχος:** Ο προσδιορισμός του επιπολασμού και του βαθμού της ΑΑ στους Έλληνες εφήβους.

**Μέθοδοι:** Το 2013, χρησιμοποιήθηκε πολυσταδιακή δειγματοληψία συστάδων για την επιλογή μαθητών Γυμνασίου ηλικίας 13 με 15 ετών σε όλη την επικράτεια. Ο εθισμός στην νικοτίνη και η ΑΑ αξιολογήθηκαν με το ερωτηματολόγιο “Hooked-on-Nicotine Checklist” (HONC). Χρησιμοποιήθηκαν μοντέλα λογιστικής και διατάξιμης παλινδρόμησης για την διερεύνηση της σχέσης μεταξύ των δημογραφικών στοιχείων των μαθητών, των καπνιστικών τους συνηθειών και της απώλειας αυτονομίας.

**Αποτελέσματα:** 339 ενεργοί καπνιστές απάντησαν στο ερωτηματολόγιο HONC (ποσοστό ανταπόκρισης: 72,2%). 51,2% ήταν αγόρια και 88,8% ανέφεραν τουλάχιστον ένα σύμπτωμα ΑΑ. Μέση βαθμολογία: 4,13/10 (Δ.Ε.95%: 3,82-4,45). Υψηλότερη βαθμολογία συσχετίστηκε αρνητικά με χαμηλότερη καπνιστική συχνότητα [αθροιστικός λόγος απόδοσης (αΛΑ): 0,240, Δ.Ε.95%: 0,144-0,400] και συσχετίστηκε θετικά με χαμηλότερη ηλικία έναρξης του καπνίσματος (αΛΑ: 2,29, Δ.Ε.95%: 1,38-3,82). Το θηλυκό φύλο είχε σημαντική συσχέτιση με μη μηδενική βαθμολογία στο HONC (σταθμισμένος ΛΑ: 2,54, Δ.Ε.95%: 1,18-5,43).

**Συμπεράσματα:** Το συχνό κάπνισμα και η χαμηλή ηλικία έναρξης του καπνίσματος σχετίζονται με υψηλότερα επίπεδα ΑΑ. Η σχέση φύλου και ΑΑ δεν είναι τόσο ξεκάθαρη.

## ABSTRACT

**Background:** Nicotine dependence constitutes the main reason for the continuation of smoking among adolescents. Loss of autonomy (LOA) is considered the epitome of dependence. Little is known regarding LOA among Greek adolescents.

**Aim:** To determine the prevalence and degree of LOA in this population.

**Methods:** In 2013, middle-school students in Greece were selected by employing multi-stage clustered sampling. Nicotine dependence and LOA were evaluated with the Hooked-on-Nicotine Checklist (HONC). Multiple logistic and ordinal regression was used to assess the association between adolescent demographics, their smoking habits and loss of autonomy.

**Results:** 339 current smokers aged 13-to-15-year-old responded to the HONC questionnaire (response rate: 72.2%). 51.2% were male and 88.8% reported at least one symptom of LOA. The mean HONC score was 4.13/10 (95%CI: 3.82-4.45). Higher HONC scores were negatively associated with lower smoking frequency [cumulative odds ratio (cOR): 0.240, 95%CI: 0.144-0.400] and positively associated with lower age at first cigarette (cOR: 2.29, 95%CI: 1.38-3.82). Female gender was significantly associated with a positive HONC score (adjusted OR: 2.54, 95%CI: 1.18-5.43).

**Conclusions:** Frequent smoking and those initiation of smoking at a younger age was associated with higher levels of LOA. The relationship between gender and LOA is not very clear.

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# INTRODUCTION

## Background on smoking and nicotine dependence

Smoking constitutes the single most preventable cause of disability and death (1). It is also the single most important cause of cancer, and lung cancer in particular, in the general population (2). In addition, smoking is one of the most significant causes of pulmonary problems including asthma and chronic obstructive pulmonary disease (3). It is strongly associated with the development of cardiovascular diseases (4) and has been reported as an associated cause of several other health problems in both genders and for all ages (5-7).

One of the most disturbing findings of smoking-related research around the globe is the gradual decrease in the age of smoking initiation, reported in children as young as 7 years old, despite strong societal efforts to limit advertisement and marketing of smoking products to underage children (8, 9). Several studies have shown that the lower the age of smoking initiation among children, the higher the risk of becoming a regular smoker in adolescence and adulthood, the higher the risk of being a heavier smoker and the harder for a smoker to quit (10, 11). Along with the above findings, research shows that experimentation with cigarettes in young children leads to the development of nicotine addiction at an early stage and subsequent difficulty in quitting (12-16).

At this point, it is pertinent to the discussion to clarify the distinction between addiction and dependence. Nicotine addiction is a behavioural disorder which involves the compulsive exposure to nicotine, due to its rewarding brain stimuli, despite its adverse consequences. Nicotine dependence, also known as withdrawal syndrome, is a state in which the individual develops unpleasant symptoms upon cessation of repeated nicotine use. Addiction and dependence may exist independently of one another (more rarely) or may occur simultaneously (more often). In both cases, the individual may find it difficult to quit smoking despite his intention to do so. Dependence may characterised by loss of autonomy (LOA) (17-19). From this perspective, studies show that adolescents who smoke occasionally, even fewer than one cigarette per day, may develop nicotine dependence and LOA, as assessed by validated questionnaires, such as the Hooked-on-Nicotine Checklist (HONC) (20, 21). Endorsing a single item on the checklist indicates some degree of LOA, which increases as more items are endorsed. Specifically,

adolescents who smoke even fewer than one cigarette per month have reported symptoms of LOA (22).

The HONC questionnaire was distributed in Greece in parallel with the Global Youth Tobacco Survey (GYTS), which is a standardised smoking-related survey that has been used worldwide to monitor smoking prevalence and associated risk factors among adolescents. Greece has one of the highest prevalence of adult smokers (38.2% current smokers) in Europe and globally (23). GYTS surveys conducted in Greece had shown that the prevalence of smoking (10.1% current users) and the prevalence of use of other nicotine products among adolescents were also quite high (24, 25). The purpose of including the HONC questionnaire was to determine the prevalence and the extent of LOA symptoms among 13-to-15-year-old adolescent smokers in Greece and investigate the association between LOA and either participant demographics or their smoking habits. The study only included students who reported use of conventional tobacco cigarettes.

**Background on statistical methods**

Various methods of analysis are employed in the studies which investigate nicotine dependence and loss of autonomy in smokers. The nature of the variables included in the models can often affect the results, especially in the case of scores like HONC. For this reason, it would be interesting to investigate the relationship between the exposure variables and the outcome variable (the HONC score) using linear regression, ordinal regression and binary logistic regression. Each model produces different coefficients and each of them must be interpreted differently. This will allow for comparison of this study's results with any HONC study, regardless of whether it analysed HONC as a continuous, ordinal or binary variable. The main focus of this dissertation will be the statistical analysis of the data.

**Linear regression models** are models which quantify the relationship between a linear outcome variable and a number of predictor variables (linear and non-linear). The equation describing linear regression is:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \cdots$$

where *y* represents the value of the outcome variable for given values of the predictor variables. $x_1$, $x_2$ etc. are the predictor variables and each of $\beta_1$, $\beta_2$ etc. is the coefficient for each predictor variable. The interpretation of a coefficient is that for an increase in its predictor variable ($x_i$) by one unit, the outcome variable increases by $\beta_i$ units. The constant term, $\beta_0$, is the value of *y* if all predictor variables had a value of zero. This does not always make sense in the natural world, but it is a useful theoretical concept used by convention in biostatistics.

Linear regression models are very powerful models for establishing correlation between variables and quantifying their relationship. However, they require many assumptions to be satisfied, including the following:

- normality of errors
- constant variance (homoscedasticity) of errors
- the population mean of errors must be zero
- no autocorrelation of errors
- no multi-collinearity
- no extreme values
- no influential observations

Because it is often difficult for these assumptions to be met, other regression models have been developed, in which the outcome variable is not linear. This decreases the strength of the conclusions that may be drawn, but makes it feasible to detect associations for which a linear model would not be appropriate.

**Binary logistic regression models** are models which determine the relationship between a binary outcome variable and a number of predictor variables. The relationship between each predictor and the outcome is described by the odds ratio. The odds are defined as a ratio of complementary probabilities, i.e. $\frac{p}{1-p}$. The odds ratio is the ratio of two odds. The equation for logistic regression is:

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \cdots$$

in which *y* is the natural logarithm of the odds of achieving the outcome compared to not achieving it, $x_1$, $x_2$ etc. are the predictor variables and each of $\beta_1$, $\beta_2$ etc. is the natural logarithm of the odds ratio for each predictor variable. Essentially, the higher the odds

ratio, the stronger the association between predictor and outcome. In order to calculate the odds ratio for variable $x_i$, we must simply exponentiate the coefficient: $\widehat{OR} = e^{\beta_i}$. The constant term, $\beta_0$, is the natural logarithm of the odds of achieving the outcome when all predictor variables have a value of zero. In the case of categorical variables, this happens when they are equal to their (arbitrarily chosen) reference category. This may or may not be a meaningful value in the natural world, e.g. if we constructed a model with gender ($x_1$) and smoking status ($x_2$) as predictors, the value of $\beta_0$ may be the value of the outcome when gender is female and smoking status is non-smoker. But if one of the predictors is a continuous variable, such as weight, the value of $\beta_0$ would not have a natural meaning.

**Ordinal regression models** are models in which the outcome variable is an ordinal variable, i.e. a variable with three or more ranked (ordered) categories or levels. The relationship between each predictor variable and the outcome variable is described by the cumulative odds. A binary model would be based on the odds of an individual being at or above a given threshold, compared to being below the threshold. The cumulative odds model is a model that calculates the odds across all cumulative splits of the ordinal outcome variable. Therefore, it is essentially a model which uses a single figure, the cumulative odds, to sum up the odds which would arise by dichotomising the ordinal outcome variable at every single level.

The equation for this model is:

$$y = \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \cdots$$

where *y* is the natural logarithm of the cumulative odds of achieving higher levels of the outcome. $x_1$, $x_2$ etc. are the predictor variables and $\beta_1$, $\beta_2$ etc. are the natural logarithms of the cumulative odds ratio for each predictor variable.

Put another way, ordinal regression combines several binary logistic models into a single model. This is only appropriate if the data satisfy certain assumptions, in order to make the use of an ordinal regression model more meaningful. This includes the assumption of proportional odds, also known as the assumption of parallel lines. This assumes that the predictor variables have the same effect on the odds, regardless of the threshold chosen. For example, for an outcome with three levels, the odds ratio of

achieving level 2 or above, for boys compared to girls, should not differ significantly from the odds ratio of achieving level 3 or above, for boys compared to girls.

**Main hypotheses**

1. Do different groups of Greek adolescent smokers have different mean HONC scores? (such groups are distinguished based on age or sex or age at first cigarette or smoking frequency or the presence smoking in the family)
2. Is there a different prevalence of LOA (defined as a HONC score of 1 or more) among different groups of Greek adolescent smokers?
3. Does the likelihood of having high, low or no LOA differ among different groups of Greek adolescent smokers? (High LOA: HONC score of 6-10; low LOA: HONC of 1-5; no LOA: HONC score of 0)

## METHODS

**Study population**

The survey was conducted in Greece across the whole country in 2013. The study population consisted of middle-school students aged 13 to 15 years old attending public or private schools (26). The selected schools were evenly split between Athens and the rest of the country. Although both smokers and non-smokers replied to the questionnaire, the focus of this dissertation is on smokers. An ever smoker was defined as anyone who had ever smoked a cigarette at least once in their life. A current smoker was defined as anyone who had smoked a cigarette at least once in the last 30 days. Within the framework of this study, loss of autonomy was investigated by focusing specifically on current smokers. Participants were included in the analysis only if they claimed to be current smokers of conventional tobacco cigarettes. The use of other nicotine products, such as pipes, cigars and electronic cigarettes, was not part of the inclusion or exclusion criteria.

**Data collection**

Data were collected using a school-based, self-administered, pencil-and-paper survey questionnaire, which included several questions on students' demographics and

their families, questions on tobacco smoking and the use of other nicotine products. The questionnaire made a clear distinction between various categories of nicotine products: tobacco cigarettes, other combustible tobacco products (pipes, cigars), non-combustible products (chewed tobacco) and electronic cigarettes. Furthermore, it contained questions pertaining to exposure to tobacco advertising, awareness of the health effects of tobacco and nicotine addiction.

**Predictor variables**

All predictor variables used in the analysis were derived from questionnaire items and, if necessary, converted to binary variables. The following variables were used: student age, gender, age at smoking initiation, number of cigarettes smoked per day during the last month and smoking in the family. Age had three categories: 13, 14 and 15 years old. Number of cigarettes smoked per day was dichotomised: $\leq 5$ cigarettes, $> 5$ cigarettes. Age at smoking initiation was also dichotomised: 11 or younger, 12 or older. A final question asked about whether parents and siblings smoked (multiple-choice question), but this was also converted to dichotomous (no one or at least one family member).

**Outcome**

Loss of autonomy (LOA), derived from the Hooked-on-Nicotine Checklist (HONC), was used as the study outcome. The questionnaire consists of 10 yes/no questions evaluating LOA in association with smoking. The HONC score was equal to the number of yes responses to the 10 questions. The HONC score, denoting LOA, was used as a continuous variable (0-10) and was also converted into a dichotomous ($0, \geq 1$) and a trichotomous variable (0 vs. 1-5 vs. 6-10). Many others who have studied LOA using HONC, including the original researchers, analysed it as a dichotomous score in the same fashion as above. In order to allow for comparisons with those studies, the same has been done in this study. This binary variable is useful since it signifies the prevalence of LOA, regardless of severity. However, is it hypothesised that the trichotomous score conveys additional, clinically relevant information (no dependence, weak dependence, strong dependence).

**Statistical Analysis**

Prior to any statistical analysis, a weighting factor was applied to reflect the probability of sampling of each student (26). The weightings were calculated using this formula: $W_i = W1 \times W2 \times f1 \times f2 \times f3 \times f4$, where:

- W1: the inverse probability of selecting the school
- W2: the inverse probability of selecting the classroom within the school
- f1: a school-level non-response adjustment factor calculated by school size category (small, medium, large)
- f2: a class-level non-response adjustment factor calculated for each school
- f3: a student-level non-response adjustment factor calculated by class
- f4: a post-stratification adjustment factor calculated by grade.

Individual weights were then scaled down, so that the size of the sample would remain the same for the purposes of the statistical analysis. Therefore, the final weight for each participant was calculated using the formula: $W_{final} = \frac{W_i \times n}{\sum_{i=1}^{n} W_i}$, where $W_i$ is the initial weight calculated for each participant, *n* is the total number of participants and $\sum_{i=1}^{n} W_i$ is the sum of all initial weights.

After applying the weights, a frequency analysis was performed and then three univariate models were developed. For the first model, which used the continuous HONC score as the outcome, it was determined that the outcome variable did not follow a normal distribution; therefore, the appropriate non-parametric test (Mann-Whitney U or Kruskal-Wallis) was used for each simple univariate analysis. However, the multiple univariate analysis, to be developed using factorial analysis of variance (ANOVA), was abandoned since the outcome variable did not follow a normal distribution. For the second model, the trichotomous HONC score was used as the outcome. Pearson's chi-square t-test was used for all simple univariate analyses. For the multiple univariate analysis, multiple ordinal regression was used in order to account for potential confounders. Finally, the third model used a binary outcome variable (HONC = 0 vs HONC ≥ 1). Potential interactions were investigated using an EVW hierarchical model, but none of the interactions were statistically significant and were thus excluded. Initially,

all aforementioned predictor variables were included in each model and justification was given wherever a predictor was excluded.

All statistical tests were performed using a two-tailed significance level of 0.05. Point estimates were accompanied by 95% confidence intervals (95% CI). Missing values were ignored. IBM® SPSS® Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA) was used for all statistical tests.

### Ethical approval

The parents of all participants were informed by mail and students verbally consented to participating in the study. The protocol of the study was approved by the Ministry of Education and Religious Affairs and by the Institutional Review Board of the National School of Public Health (NSPH) in Athens, Greece.

## RESULTS

A total of 4,096 students aged 13-15 years old responded to the overall survey, of which 412 were current smokers, i.e. they reported having smoked at least once in the last 30 days (prevalence: 10.1%). Among this group, 339 students responded to the HONC questionnaire (response rate: 82.3%) and were included in the analysis. About 15.8% of HONC respondents were 13 years old, 37.6% were 14 years old and 46.6% were 15 years old. A total of 51.2% were male and 88.8% reported at least 1 symptom of LOA based on HONC. Nearly all participants reported that other members of their family smoked (99.8%); therefore, this variable was excluded from any further analysis due to its low variability. The mean HONC score was 4.13/10 (95% CI: 3.82-4.45). The distribution of the predictor variables is presented in Table 1, while the distribution of HONC scores is presented (for both sexes together and separately) in Figure 1.

**Table 1: Frequency analysis of population characteristics**

| | | Point estimate | 95% CI | | n |
|---|---|---|---|---|---|
| **HONC score categories** | 0 | 11.2% | 7.84% | 14.5% | 339 |

| | | | | | |
|---|---|---|---|---|---|
| | 1-5<br>6-10 | 56.5%<br>32.3% | 51.2%<br>27.3% | 61.8%<br>37.3% | |
| **Age** | 13 years<br>14 years<br>15 years | 15.8%<br>37.6%<br>46.6% | 11.9%<br>32.4%<br>41.3% | 19.7%<br>42.7%<br>51.9% | 339 |
| **Gender** | Boys<br>Girls | 51.2%<br>48.8% | 45.9%<br>43.5% | 56.5%<br>54.1% | 339 |
| **Cigarettes per day** | ≤ 5 cigarettes<br>> 5 cigarettes | 70.7%<br>29.3% | 65.8%<br>24.4% | 75.6%<br>34.2% | 329 |
| **Age at first cigarette** | 11 or younger<br>12 or older | 26.7%<br>73.3% | 22.0%<br>68.5% | 31.5%<br>78.0% | 334 |
| **Smoking in the family** | No<br>Yes | 0.2%<br>99.8% | 0.0%<br>99.3% | 0.72%<br>100.0% | 339 |

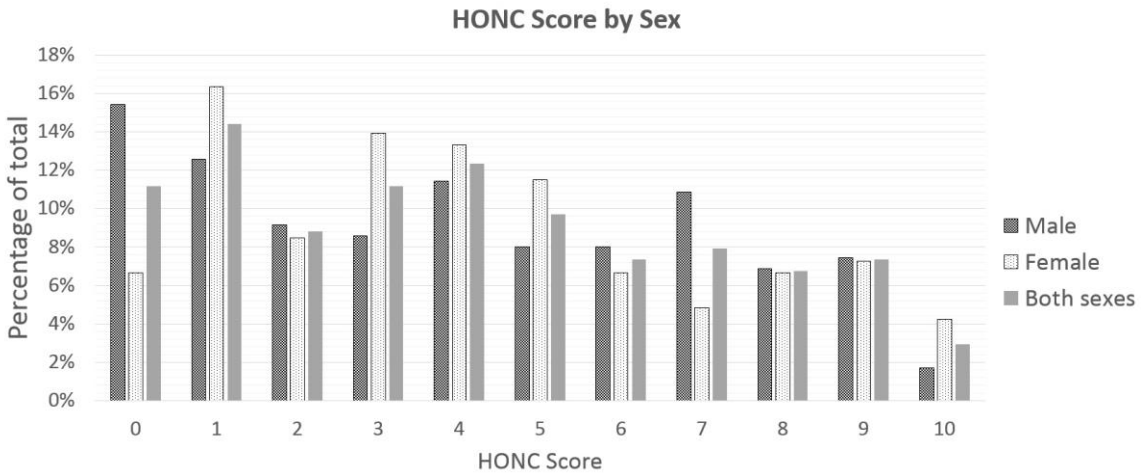


**Figure 1: Distribution of Hooked-on-Nicotine Checklist scores by sex**

In Table 2, the results of the simple univariate analysis are presented. A significant difference between the median values of the continuous HONC score was found when comparing those who smoked five or less vs. more than five cigarettes per day, with the latter group reporting higher scores. The same was found when comparing

those that initiated smoking at age 11 or younger as compared to those at age 12 or older, with the prior group reporting higher scores. The same variables were significantly associated with the HONC score when it was converted into a trichotomous variable.

**Table 2: Simple univariate analysis of the association between predictors and LOA (0 vs. 1-5 vs. 6-10)**

| **Outcomes:** | **Score (0-10)** | | **Loss of autonomy (LOA)** | | | |
|---|---|---|---|---|---|---|
| **Predictors** | **Median** | **p-value** | **Proportions** | | | **p-value** |
| | | | **0** | **1-5** | **6-10** | |
| **Age** | | | | | | |
| 13 years | 5 | 0.786 | 18.9% | 39.6% | 41.5% | 0.053 |
| 14 years | 4 | | 8.7% | 57.5% | 33.9% | |
| 15 years | 3.6 | | 10.8% | 61.4% | 27.8% | |
| **Gender** | | | | | | |
| Boys | 4 | 0.425 | 15.5% | 50.0% | 34.5% | 0.11 |
| Girls | 4 | | 6.7% | 63.4% | 29.9% | |
| **Age at 1st cigarette** | | | | | | |
| 11 or younger | 6 | 0.003* | 7.9% | 41.6% | 50.6% | <0.001* |
| 12 or older | 4 | | 12.7% | 61.6% | 25.7% | |
| **Cigarettes per day** | | | | | | |
| ≤ 5 cigarettes | 3 | <0.001* | 14.2% | 63.1% | 22.7% | <0.001* |
| > 5 cigarettes | 6 | | 2.1% | 41.7% | 56.3% | |

*Significant p-values are denoted with an asterisk.

Table 3 contains the results of the ordinal regression which investigated the association between the trichotomous HONC score (0 vs. 1-5 vs. 6-10) and two predictors: smoking frequency and age of smoking initiation. The cumulative odds ratio (cOR) of scoring a higher HONC score for those who smoked less compared to those who smoked more frequently was 0.240 (95% CI: 0.144-0.400), which suggests a positive association between higher smoking frequency and higher LOA. On the other

hand, the cOR of scoring a higher HONC score for those who started smoking at or below 11 years old was 2.29 (95% CI: 1.38-3.82), compared to those who started smoking at or above 12 years old, which suggests a positive association between lower age of smoking initiation and higher LOA. Both associations were statistically significant. The inclusion of age and sex in the ordinal regression model was also explored; however, it was decided to omit these two variables. The main reason was that their inclusion resulted in a violation of the assumption of proportional odds; however, in addition to this, their association with the outcome was non-significant.

**Table 3: Multiple univariate analysis of the association between predictors and LOA (HONC = 0 vs. 1-5 vs. 6-10)**

| **Outcome:** | | **Loss of autonomy (LOA)** | | |
|---|---|---|---|---|
| **Predictors** | | **cOR** | **95% C.I.** | **p-value** |
| **Age at first cigarette** | 11 or younger<br>12 or older | 2.29<br>ref. | 1.38-3.82 | 0.001* |
| **Cigarettes per day** | ≤ 5 cigarettes<br>> 5 cigarettes | 0.240<br>ref. | 0.144-0.400 | <0.001* |

*Significant p-values are denoted with an asterisk.

Finally, a separate analysis was carried out using multiple binary logistic regression, as seen in Tables 4 and 5. The outcome variable was a dichotomous HONC score (0 vs ≥ 1). Table 4 shows the results of the initial model, where the basic variables and their interactions were included. Since all interactions were non-significant, they were removed one-by-one, leading to the model in table 5.

**Table 4: Multiple univariate analysis of the association between predictors and LOA (HONC = 0 vs. 1-10) – INITIAL MODEL**

| **Outcome:** | **Loss of autonomy (LOA)** |
|---|---|
| **Predictors** | **p-value** |

| | |
|---|---|
| Age (1) | 0.968 |
| Sex (2) | 0.869 |
| Age at first cigarette (3) | 0.865 |
| Cigarettes per day (4) | 0.432 |
| 1*4 | 0.977 |
| 2*4 | 0.608 |
| 3*4 | 0.978 |

*Significant p-values are denoted with an asterisk.

As seen in Table 5, it was found that female gender [adjusted odds ratio (aOR): 2.54, 95% CI: 1.18-5.43] and daily smoking frequency (aOR: 6.34, 95% CI: 1.61-25.1) were significantly associated with a positive HONC score, while the student's current age and the student's age at smoking initiation were not.

**Table 5: Multiple univariate analysis of the association between predictors and LOA (HONC = 0 vs. 1-5 vs. 6-10)**

| **Outcome:** | | **Loss of autonomy (LOA)** | | |
|---|---|---|---|---|
| **Predictors** | | **cOR** | **95% C.I.** | **p-value** |
| **Age** | 15 years old<br>14 years old<br>13 years old | 2.26<br>2.48<br>ref. | 0.907-5.62<br>0.957-6.43 | 0.080<br>0.061 |
| **Sex** | Female<br>Male | 2.54<br>ref. | 1.18-5.43 | 0.017* |
| **Age at first cigarette** | 11 or younger<br>12 or older | 0.713<br>ref. | 0.287-1.77 | 0.465 |
| **Cigarettes per day** | ≤ 5 cigarettes | 6.34 | 1.61-25.0 | 0.008* |

| | | | | |
|---|---|---|---|---|
| | > 5 cigarettes | ref. | | |
| **Constant:** | | 2.67 | N/A | 0.061 |

*Significant p-values are denoted with an asterisk.

# DISCUSSION

### Interpretation of results and comparison with other studies

This is the first study to examine the association between the extent of smoking and loss of autonomy (LOA) among adolescents in Greece. It was found that a relatively high prevalence of LOA exists among 13-to-15-year-old smoking adolescents in Greece (88.8%). The mean HONC score of 4.13/10 indicates that the degree of LOA is similar to that reported for current adolescent smokers in other countries. In Romania (27), for example, in a group of 14-to-16-year-old students, the HONC score was 3.4-3.5/9 (which is equal to 3.8-3.9/10). On the other hand, the degree of LOA was found to be lower in one cross-sectional study from Florida (28) among 14-to-18-year-old students, with a mean HONC score of 2.8/10, as well as among 13-to-17-year-old students in Malaysia (29), with a mean HONC score of 2.7/10; however, the latter survey also included exclusive users of electronic cigarettes (EC). With the exclusion of EC-exclusive users, the prevalence of LOA increased from 78.7% to 90.6%, which is similar to the observed prevalence in the current study. A study in New Zealand (30) also found a similar prevalence of LOA among 13-to-17-year old students (87.9%), while the mean HONC score was slightly higher (4.9/10, SD: 3.3). A study among 14-to-17-year-olds in France (31) found a much higher mean score (5.5/10) and a higher prevalence of LOA (93.8%), but this was expected since it was carried out among daily smokers, not current smokers.

Two interesting findings, consistent with the results of other studies (17, 30), are that students who began to smoke at a younger age and students who smoked more frequently had significantly higher degrees of LOA. This raises further concerns about the effects of nicotine on the child and adolescent brain. The results of this and other studies point to the possibility that physical or mental dependence becomes more hard-wired and more permanent if the brain is exposed to addictive substances at an earlier developmental stage. The power of habit itself, whether addictive or not, must also not be

understated: the earlier a habit is adopted, the harder it is to overcome. An important factor not explored in most of these studies is the use of other nicotine products. If any reliable conclusions are to be drawn about youth nicotine dependence at the population level, total nicotine intake would be pertinent to this matter since conventional cigarettes are only one of many sources of nicotine.

Furthermore, it was possible to replicate the results of other studies which found that girls had a significantly higher prevalence of LOA (HONC $\geq 1$) compared to boys, despite having lower levels of smoking. This was a repeated finding across different countries and cultures (17, 18, 22, 32). However, it is noteworthy that the association between female gender and LOA was not significant when dividing the HONC score into three categories. Indeed, it is apparent from figure 2 that there is a big difference between boys and girls at HONC=0, but this does not remain consistent across the spectrum of HONC scores. As seen in Table 2, there are more boys than girls in the 'no dependence' category but there are also more boys than girls in the 'strong dependence' category. Girls are more abundant in the 'weak dependence' category. Therefore, it seems that boys are more likely to occupy the ends of the spectrum and girls are more likely to occupy the middle.

The choice of statistical model has a significant effect on the results, as well as their interpretation. A linear model would have been ideal since it would have provided a quantitative relationship between the predictors and the outcome. As this was not possible in the case of the HONC questionnaire results, ordinal and logistic regression models were used instead, which allow for qualitative or semi-quantitative interpretations of the results. It is possible to speak about the relative strength of associations, without being able to determine their nature (causal or confounding) or the absolute effect of the predictors on the outcome. This may explain the apparent discrepancies in the results, such as that the age at first cigarette was significantly associated with the outcome in the ordinal regression model but not in the binary logistic model. The ordinal HONC outcome contained different information to the binary HONC outcome; it is not clear whether the prevalence of LOA alone is sufficiently clinically meaningful or whether the degree of LOA conveys necessary additional information. The results of this study seem to support the latter conjecture.

## Limitations

Limitations of this study include its cross-sectional design, which does not allow for causal inferences with regard to the identified associations. Furthermore, approximately 82% of respondents who claimed to be current users of conventional cigarettes responded to the HONC questionnaire. This response rate is sufficiently high; however, it is not possible to exclude the possibility of selection bias since refusal to respond may have been related to the student's smoking status and LOA. Moreover, it is possible that prevalence of nicotine product use was under-reported. Since the study relies on self-reported data, there may be recall bias or social desirability bias, with students being reluctant to admit their smoking or symptoms of nicotine dependence. In addition, not all children in Greece aged up to 15 are enrolled in school. Smoking prevalence is speculated to be higher among children who do not attend school. For the above reasons, it is expected that the true prevalence of smoking and of LOA symptoms among middle-school adolescents in Greece would be higher than estimated. It is also speculated that boys are more likely to drop out of school. It is possible that, if boys are more likely to smoke and if they are underrepresented in this survey, then the gender differences identified in this study may not be representative of Greek adolescents overall.

## Synopsis

In summary, a high prevalence of LOA was found among adolescent Greek smokers. Those who smoke more frequently and those who started smoking at a younger age were found to have higher levels of LOA. Girls also had a greater tendency to exhibit LOA compared to boys. It is important to find effective ways to prevent children from smoking and to identify the effective strategies for dealing with nicotine dependence and LOA, as this will mitigate the negative consequences at an individual and at a population level. Policy makers should take the above findings into consideration given that smoking initiation occurs at a very early age, thereby trapping young children into a vicious cycle of dependence and LOA with severe negative health projections for the rest of their lives.

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